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Epidemiological Evidence of Carcinogenicity of Chlorinated Organics in Drinking Water

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Concern has recently been voiced over possible chronic toxicity associated with chlorination of public drinking water supplies in the United States. This paper reviews the available evidence and the studies underway to further evaluate hypothesized associations between cancer risk and byproducts of chlorination. Preliminary data from measures of halogenated volatiles and personal exposure histories from respondents in a large epidemiologic study of bladder cancer are presented. These data support the use in epidemiologic studies of categorical measures of exposure and suggest that results from completed case-control studies, based on death certificates, may have underestimated the true risk of exposure to chlorination by-products. The current generation of studies which use a case-control interview design offer many advantages over earlier efforts to evaluate this issue.

Introduction

Chlorination of public drinking water supplies in the United States was first practiced in 1908 at the Boonton, New Jersey waterworks supplying Jersey City (*1,2*). Chlorination was initiated in response to a legal challenge that the water utility had not been meeting its contracted obligation to supply water pure and wholesome to drink. In reviewing the facts in May, 1910, after chlorination had been in place for more than a year, the judge noted that chlorination was quite effective in destroying "germs" and thereby improving the quality of the drinking water. He added:

> Upon the proofs before me, I also find that the solution described leaves no deleterious substances in the water. . . . I do therefore find and report that this device is capable of rendering the water delivered to Jersey City pure and wholesome, for the purposes for which it is intended and is effective in removing from the water those dangerous germs which were deemed by the decree to possibly exist therein at certain times (*1*).

In light of its obvious benefits, concern about adverse effects of chlorination rapidly diminished, and the practice spread to most large population centers of the United States within a decade. Introduction of chlorine disinfection came after two decades that had witnessed introduction of filtration, sedimentation, and coagulation to many large water supplies. These practices were themselves very effective in controlling levels of water-borne infectious bacteria.

Figure 1 shows the dramatic decrease in U.S. typhoid mortality between 1900 and 1928 (*3*). Introduction of filtration in public water supplies had already accounted for a large part of the decrease in mortality rates before the widespread use of chlorination in the years after 1910. In Cincinnati, for example, the annual typhoid rate dropped from 379 per 100,000 in 1905–1907 to 60 per 100,000 in 1908–1910 with the introduction coagulation, sedi-

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mentation and filtration of the public drinking water. The addition of a chlorination step a few years later further decreased the rate. Current studies are now attempting to quantify the health and economic benefits of chlorination.

Concern over adverse effects of chlorination was quiescent from 1910 until a few years ago. In 1974, it was reported that chloroform and other trihalomethanes could be produced from the interaction of chlorine and organic molecules such as humic and fulvic acids in the raw water of drinking water supplies (*4*,*5*). A subsequent nationwide survey by the Environmental Protection Agency showed indeed that chloroform is found in almost every chlorinated supply (*6*). Concern was elevated when a National Cancer Institute animal feeding study indicated that chloroform is a carcinogen (*7*). More recently, attention has been focused on the genotoxic potential of higher molecular weight nonvolatile chlorinated organics that are also produced during chlorination (*8*).

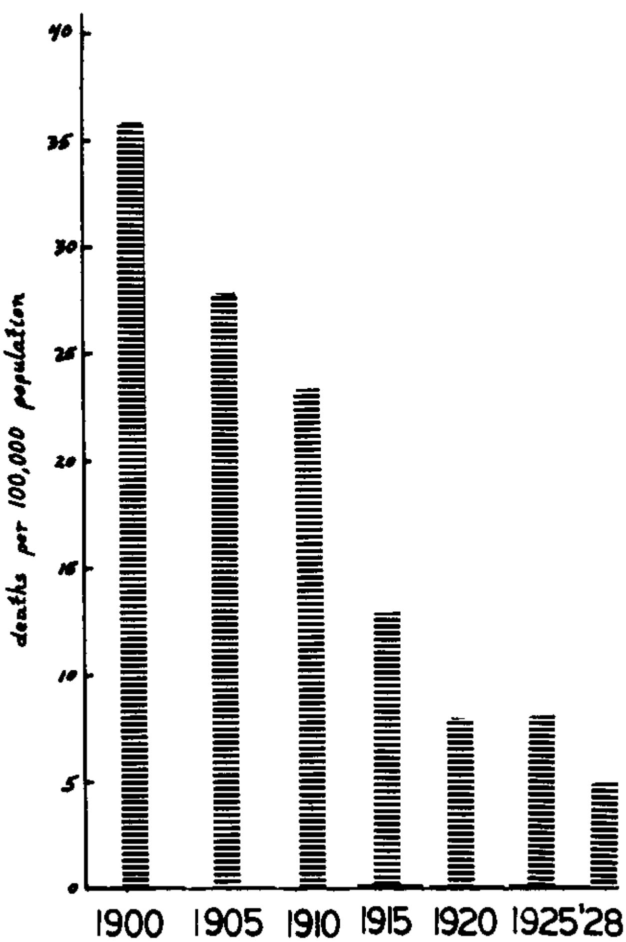

FIGURE 1. Annual U.S. typhoid mortality rates, 1900–1928.

The implications of an association of chlorination with one or more types of human cancer are immense. A recent survey from the EPA Office of Water Supply estimates that 192.2 million persons in the United States are served by community water systems (*9*). The vast majority of these systems use chlorine as a disinfectant. The health benefits to be gained by limiting, curtailing, or substituting for chlorine must be carefully balanced by considering other health risks which may result.

Measures of Exposure in Epidemiologic Studies

A lack of specific historical environmental data, especially chemical measurements, has compelled the use in epidemiologic studies of surrogate measures of past exposure to water-borne organic chemicals. Several types of water quality indicators have been used. The proportion of a county's population using surface as opposed to ground water is one, and the county population served by chlorinated sources, in contrast to nonchlorinated, is another. The percentage of a county's population served by water from a river with upstream industry may be considered a special case of the surface/ground indicator. Other water quality variables used in epidemiologic studies are trihalomethane concentration in the supply serving an individual or most of a county and the historical chlorine dose in such supplies.

An environmental data base under development in conjunction with a large-scale bladder cancer case-control study provides some insight into the categorical exposure measures of epidemiologic studies. Collection of this data was supported by the Cincinnati Health Effects Research Laboratory of the Environmental Protection Agency. The first completed data come from the state of Iowa, one of ten areas of the United States in this study. We collected information and samples from 289 water sources used by 238 utilities. Of the 256 ground sources, 51 are not chlorinated, and these are found exclusively in small towns. Although surface sources represent but 11% of the total number of sources, they serve 23% of the population using community supplies. Almost 2 million Iowa residents are served by community supplies serving 1,000 people or more, and the remaining million residents use water from very small community sources or from their own private wells.

Chloroform Dose and Chloroform Levels

Figures 2–6 show data on chloroform levels and chlorine dosage in the ground and surface sources of Iowa. Levels of nonvolatile chlorinated compounds of higher molecular weight tend to vary with chloroform levels, so chloroform measures may be interpreted as representing a much larger class of compounds, many with demonstrated mutagenic and carcinogenic properties.

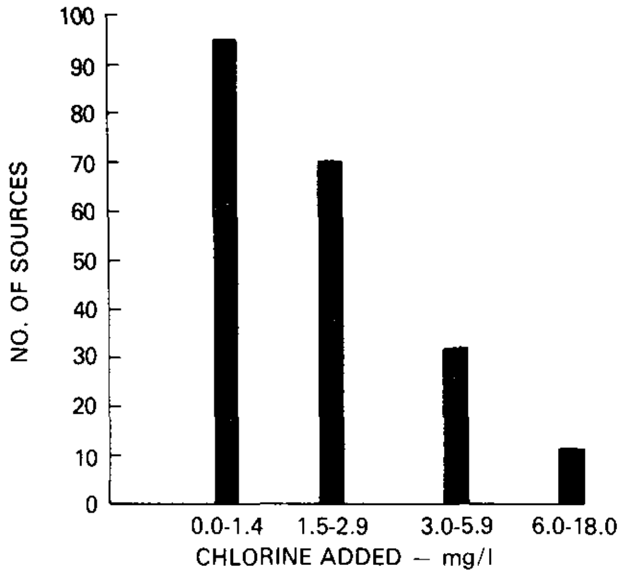

FIGURE 2. Distribution of annual average chlorine dose among ground water sources, Iowa, 1979.

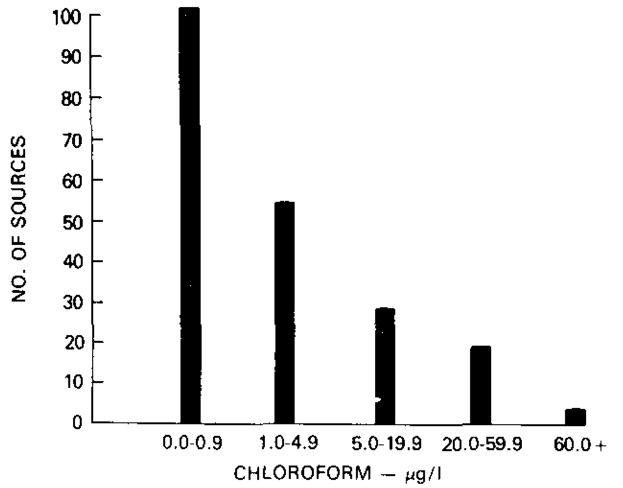

FIGURE 3. Distribution of measured chloroform levels in finished water from chlorinated ground sources, Iowa, 1979.

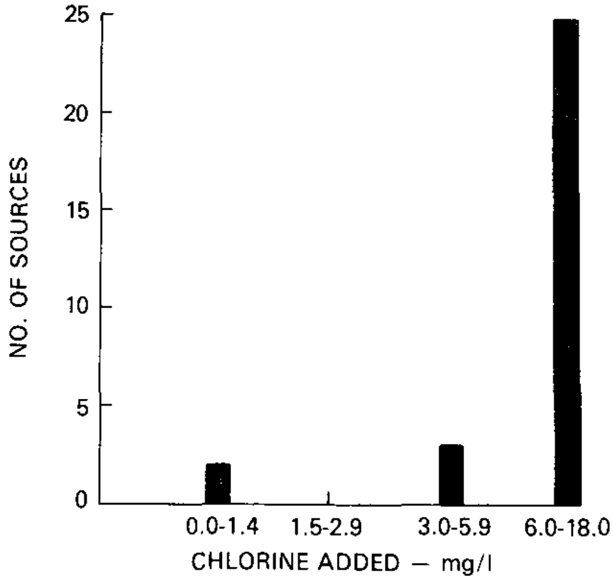

FIGURE 4. Distribution of annual average chlorine dose among surface water sources, Iowa, 1979.

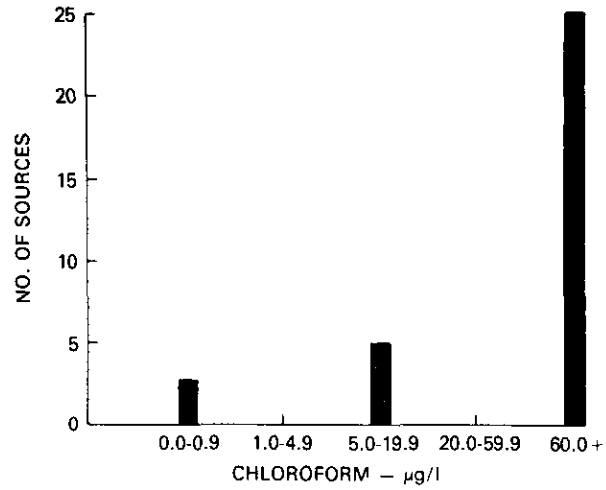

FIGURE 5. Distribution of measured chloroform levels in finished water from chlorinated surface sources, Iowa, 1979.

Figure 2 shows how many ground sources had chlorine dosages in given ranges. It demonstrates that most ground sources were treated with less than 3 mg/l., with relatively few ground sources in the higher dose ranges.

Figure 3 shows the number of these same ground sources with measured chloroform levels falling in different ranges. The distribution pattern of chloroform levels parallels the chlorine dosage pattern. Three-fourths of the samples from ground sources had chloroform levels of less than 5 μg/l.

The distribution among surface sources of chlorine dosage and measured chloroform levels provides a sharp contrast with the distribution among ground sources. Figure 4 shows how many surface sources had chlorine dosages of given levels. In contrast to ground sources, the chlorine dose in most surface sources was greater than 6 mg/l. Most U.S. water supplies observe breakpoint chlorination. That is, chlorine is added until a free residual is produced. If the raw water contains high levels of organics, more chlorine is necessary to oxidize materials before free chlorine is available.

Figure 5 shows chloroform levels among the surface sources. Surface sources tended to have elevated levels of chloroform, in contrast with ground sources, with most measuring above 60 μg/l. Half of the 33 surface sources in Iowa had chloroform levels greater than 107 μg/l.

Figure 6 shows the distribution of chloroform as a function of annual average chlorine added, in surface sources and in ground sources. Levels of both chloroform and of added chlorine are elevated in surface sources, as mentioned above. Within the surface or ground source category, however, there is no within-group association of added chlorine with measured chloroform level. This counterintuitive observation may result from the types of data we collected. "Chlorine added" is the reported average dose over the year prior to sampling, and chloroform was measured in a one-time grab sample in which the haloform reaction was allowed to go to completion. The lack of correlation between chlorine dose, and measured chloroform level, within source groups, implies that records of historical chlorine dose may not provide reliable and acceptable guides to levels of some classes of chlorination by-products in finished drinking waters. It is clear, though, that there are large differences in chlorine dose and in chloroform level (and presumably in levels of nonvolatile chlorinated compounds) between ground and surface sources. Historical dosage information would appear to provide no better a guide to the mutagenic or carcinogenic potential of organics in finished drinking water than a categorical definition of source type, such as "surface" or "ground". Evaluation of data from the other nine study areas will help clarify this issue.

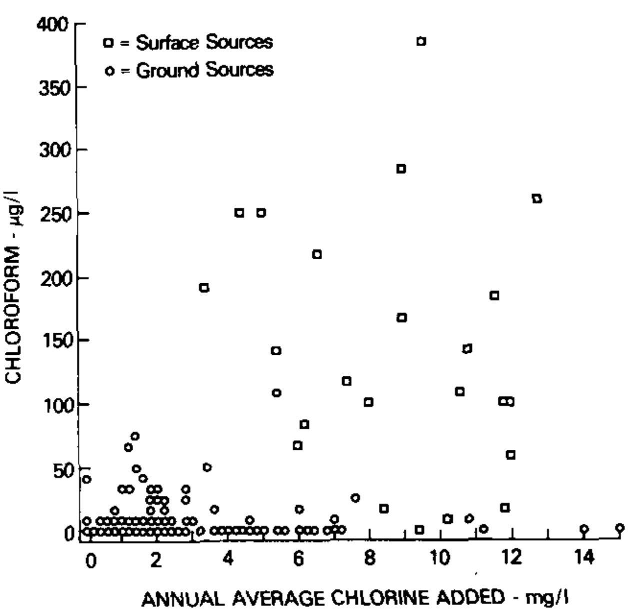

FIGURE 6. Measured chloroform levels versus chlorine dose in finished water from surface and ground sources, Iowa, 1979. Many of the points represent 2 or more measurements.

Review of Epidemiologic Studies

Since 1974, at least 20 epidemiologic studies have assessed the relation between one or more aspects of water quality and one or more forms of cancer. These studies differ markedly in design and in what they can reveal about possible water-cancer relationships. Several reviews of these studies have been prepared (*10–14*) and these will not be repeated here. The studies may be evaluated from several points of view including the general study design (ecologic or case-control), the choice of health endpoint used as a measure of effect, the use and availability of other exposure factors or host characteristics which may confound associations, and the choice of water exposure variables or surrogate variables. One major distinction to be made among the studies is between geographic correlation and case-control studies. Another distinction is between studies based on mortality measures and those based on morbidity. The great majority of completed studies are correlational studies based on mortality rates, usually aggregated on a county level.

Geographic Correlation Studies

Geographic correlational studies usually use existing data resources, and therefore may be performed rather inexpensively and rapidly. The results from such studies can serve as qualitative guides to potential environmental risk factors and the types of health impact which they may have. Following the first perception of possible cancer risks from contaminated drinking water, a number of geographic correlation studies were mounted. Most used multivariate techniques to seek associations between county cancer mortality rates and one or more surrogate measures of water quality from the predominant county drinking water supply. In most, a multiple regression model was used to adjust for county demographic and industrial characteristics known or thought to be related to the malignancy under study. The dependent variable in each model was a rate, specific for sex and race. Calculated values of the regression coefficients estimated the relative contributions of the "independent" variables to the cancer rate.

Three geographic correlation studies provide examples of the different types of surrogate exposure variables that have been used. Page and co-workers (*15*) addressed the issue of whether county parish populations in Louisiana served by the Mississippi had higher cancer rates than other parishes. The water exposure variable was the percentage of a parish's population using Mississippi water, and it was included in the regression model along with several variables for parish industrial and socioeconomic characteristics.

Salg (*16*) examined data from the 346 counties of the Ohio river drainage basin. The exposure index in one analysis was the percent of a county's population served by surface water, and in another, the percent with pre-chlorinated water. Each county cancer mortality rate, specific for sex and race, was regressed on the water exposure variable and several county demographic and industrial variables.

Cantor et al. (*17*) looked at cancer rates in counties with water supplies sampled by the Environmental Protection Agency in 1975. The multivariate analyses were restricted to the 76 counties with more than 50% of their population served by the sampled supply. The exposure was one of three continuous variables: the total trihalomethane level; the chloroform concentration; or the brominated trihalomethane level. Several demographic, socioeconomic, and industrial characteristics of the study counties were included in the regression model.

The primary purpose of the correlational study is hypothesis generation; that is, a preliminary evaluation to determine if more detailed studies might be warranted. Inferences from correlational studies are limited because information on such potentially important factors as migration and historical exposure patterns is often incomplete or nonexistent. The measure of effect is the county cancer rate, a group characteristic, and not the particular experience of individual group members. Individuals who die of cancer may not be the most highly exposed members of the population. Information is often missing on other factors related to the risk of disease, such as cigarette smoking, and an observed association may be due to the confounding influence of these uncontrolled variables. Positive associations from such studies must therefore be interpreted with caution since they may not reflect a cause-effect relationship.

The suspicion that a causal relationship may underly statistical associations is increased, however, if several independent studies observe similar patterns of correlation in different regions, among different populations, and in both sexes. A report by the National Academy of Sciences (*10*) and more recent reviews by Wilkins et al. (*11*) and by Shy and Struba (*12*) are in general agreement that results from ecologic and case-control studies point to possible associations for bladder, rectal, and colon cancer. In a review completed in 1978, we noted consistencies in geographic associations between bladder cancer and drinking water quality (*13*). Among the eleven studies we reviewed, eight revealed positive and statistically significant associations among white males between bladder cancer rates and one or another measure of drinking water contamination.

Case-Control Studies

Case-control studies, which use information on individuals, can provide quantitative estimates of risk. The basic approach is to gather personal histories for persons with the disease of interest and for a series of matched individuals without the condition (controls). Estimates of risk derive from comparisons of the exposure of cases and controls. The case-control studies released to date are based on mortality records. These studies represent a major advance over ecologic studies. The drawbacks which remain derive in large part from limitations of the primary data source they use: the death certificate. Characterization of drinking water source is based on a link of water supply data to the address on the death certificate, and thus represents the last drinking water source of the decedent. Misclassification of exposure can occur if the individual had recently migrated from an area with different drinking water source characteristics. Another weakness of case-control studies based on death certificates is their inability to adjust for other exposures which may have caused the disease. The investigator is not able to control for diet or cigarette smoking, and the only occupational information available is that listed on the certificate of death. Despite these weaknesses, the case-control studies based on death certificates are a major methodologic improvement over the earlier ecologic studies, and they have provided a significant contribution to our understanding of drinking water quality and cancer.

The Council on Environmental Quality recently released a contractor's report in which five case-control death certificate studies were reviewed (*14*). The reviewers noted the consistency among the studies and positive associations between rectal, colon, and bladder cancers, and one or more water quality variables. They noted that associations with rectal cancer were observed in all five studies.

Case-Control Interview Studies: An Example

An alternative to the case-control study based on death certificates is the interview study that uses information collected directly from patients and their matched controls. At least five such studies are currently in progress (Table 1). Each is examining the association of many risk factors, among them water quality factors, with one type of cancer. The anatomic sites in these ongoing studies are those that were suggested by the completed studies: colon, rectum, and bladder. These case-control interview studies do not suffer from many of the drawbacks of mortality studies.

The suggested links between drinking water quality and bladder cancer are being pursued by incorporating a water quality component into a large case-control interview study of bladder cancer. This investigation was originally motivated by the need for information on saccharin. The case-control design permitted, and indeed required, that information on other known and suspect causes of the disease also be gathered and considered in the analysis. In this study, we interviewed 3000 persons who were newly diagnosed with bladder cancer during 1978 in five states and five metropolitan areas of the United States, and a series of 6000 controls. Age was restricted to the range 21–84. Controls aged 21–64 were chosen using a random digit dialing method. Older controls were randomly sampled from files of the Health Care Financing Agency. By personal interview, we obtained information on demographic background, smoking history, occupational history, relevant medical information and a history of artificial sweetener use. Information on several other items such as coffee drinking habits, use of hair dyes and fluid ingestion patterns were also gathered. A report on saccharin has been released (*18*).

Information from a residential and water supply history for each respondent is being used to create a lifelong water quality profile. We obtained a lifetime residential history from each participant and asked whether the primary drinking water source at each residence was community, private well, bottled, or other. Independently, we gathered data from more than 1000 public utilities in the ten study areas. We collected historical information on the raw water sources, the treatment practices, and the geographic areas served by each purveyor, going as far back as 1900. Information on water source includes whether the source is surface, ground or purchased. Surface waters are further characterized by the amount and type of potential contamination. Ground sources are characterized by the depth and number of wells and characteristics of the aquifer. If the major source of water was another water supply, the supplier is indicated and a link is then made to his records. Many types of treatment information are recorded, including mechanical treatment, chemical treatment other than chlorination, and chlorination. An attempt was made to retrieve information on chlorine dose, but in our experience, this information is often not available. A list of the geographic areas served is also collected. Some data was obtained from centralized state or federal records. In all cases, it was also necessary to visit the utilities and obtain information directly from their records or from personal interviews with utility officials.

Table 1. Case-control studies in progress.

Investigator(s) (inst./funding)	Anatomic sites	Cases/ controls	Locale	Sex/race	Completion date	Design notes
Cantor et al. (NCI/EPA/FDA)	Urinary bladder	3000/6000	10 Areas, U.S.	All	1982	Population based interview
Gottlieb (Tulane/EPA)	Colon, rectum	500/500	SE Louisiana	All	1984	Hospital based interview
Kanarek and Young (U. Wisc./EPA)	Colon	200/400	Wisconsin	WM, WF	1983/4	Population based interview
Shy and Struba (UNC/NIH)	Colon	300/600	N. Carolina	All	1982	Hospital based interview
Trock (N.Y. State)	Colon, rectum	400/400	N.Y. state (Outside N.Y.C.)	F	1982	Mortality records, confirmed diagnoses, 20 yr residential history

The potential value of these data for the bladder cancer case-control study was estimated by calculating the total years of experience spent in and out of study areas by participants and seeing for how many years they were served by a municipal source, a private well or spring, or by some other source. We were able to account for approximately 90% of the estimated total person-years of all cases and controls. Of these, 342,844 person years (62.8%) were spent within study areas on municipal supplies where we have excellent coverage of historical community supply information; 14.3% of respondent person-years were spent in areas with municipal supplies where we have limited information, or on other water sources; 109,295 respondent person-years (20.0%) were at residences where a private well or spring was the major source of drinking water. The total number of person-years spent in residences with private wells or springs or with a municipal source of water where we have the possibility of getting specific information represents approximately 452,000 person-years of experience or 75% (83% × 0.90) of the total lifetime experience of all cases and controls. This level of exposure ascertainment is well within acceptable bounds for epidemiologic evaluation.

High-speed digital computers allow the merging of historical community water supply information with the personal residential histories of study respondents. For each year, the complete record of each individual contains information on the water source type from the interview, and if the respondent indicated that a community source was used, detailed information on that drinking water source. In the first epidemiologic analyses, we are looking at just a few features of drinking water source, namely, whether the water is chlorinated or not and whether the water comes from a surface or a ground source. It is possible, of course, to return to the original utility record to pull in any additional information which is deemed important.

The types of records being created are demonstrated in Figures 7–9, which describe historical types of water source serving study participants from Iowa. Three source categories are shown: ground not chlorinated; ground chlorinated; and surface chlorinated. Figure 7 shows, for respondents who had a nonchlorinated ground source in 1975, the type of source that they had from 1910 onwards. It suggests that people on this type of source have had limited residential mobility. If exposures of importance had occurred prior to 1950, use of the 1975 drinking water source to characterize earlier exposures in an epidemiologic study would not result in important misclassification among this group. In contrast are the people in Iowa presently consuming chlorinated water. Figure 8 shows the distribution over time of the 364 respondents whose homes were served by chlorinated ground sources in 1975. Prior to 1950, fewer than half of this group were served by the same kind of water. The increase in the use of chlorinated ground water represents a shift from nonchlorinated ground water among this population. It is likely that this shift represents the increasing practice of chlorination in modest sized communities with ground sources. The use of the 1975 source definition in epidemiologic studies could lead to misclassification of exposure in this group of individuals. Figure 9 shows similar data for the 231 respondents whose source of drinking water in 1975 was a surface chlorinated source. Before 1955, less than 40% of this group were drinking chlorinated surface water. A fourth category, "other" represents the percentage that each year's total is less than 100% In the "other" category are people who reported a municipal drinking water source from outside of the study

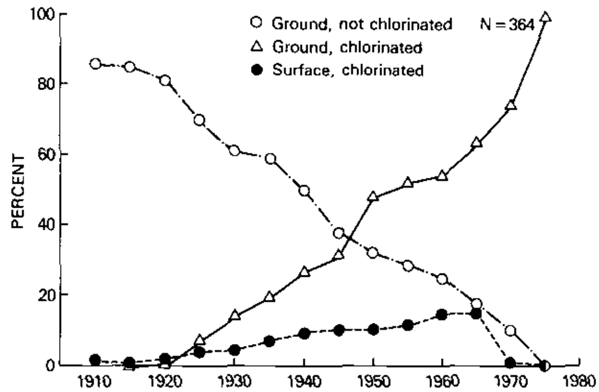

FIGURE 7. Type of water source, 1910–1975, of Iowa study respondents with a nonchlorinated ground source in 1975.

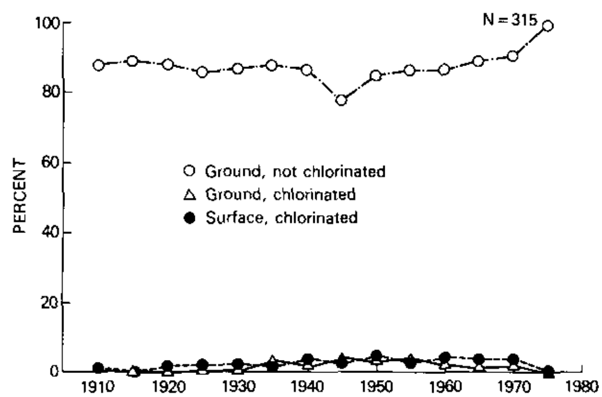

FIGURE 8. Type of water source, 1910–1975, of Iowa study respondents with a chlorinated ground source in 1975.

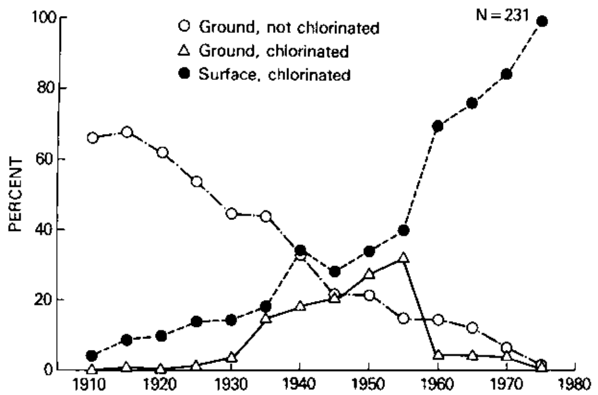

FIGURE 9. Type of water source, 1910–1975, of Iowa study respondents with a chlorinated surface source in 1975.

area, or who were among the number who had some unusual source or did not report a drinking water source for the year in question. Estimates of risk based on the 1975 water source in an epidemiologic study would likely underestimate the real risk, because the greatest shifts have been from ground, nonchlorinated to the chlorinated categories. We do not know at this time how representative the experience of the Iowa study population may be of the places where ecologic or case-control death certificate studies of water quality have been performed. These data suggest that the completed ecologic and case-control studies based on mortality data alone may have underestimated effects because of misclassification of exposure. Studies that accounted for changes in water source due to migration or to modifications in water treatment such as the work of Young (*19*) and of Gottlieb (*20*) may not be so seriously affected by the misclassification problem as some of the others.

Summary and Conclusion

The major strengths of the case-control interview study design in the evaluation of water contaminants are many. Historical exposures of individuals may be defined with a completeness and accuracy not possible in ecologic studies or in case-control studies based on mortality records.

Collection of information on a wide variety of other known and suspect risk factors permits control for these other exposures as well as measurement of interaction of them with water exposures. Let us suppose that products of chlorination did not influence the likelihood of bladder cancer, but that people served by contaminated water smoked at higher rates than people served by pristine sources. An analysis that could not adjust for smoking might mistakenly associate bladder cancer with poor water quality. Alternatively, if water-borne carcinogens were causally related to the disease and smoking data were available, then elevated risks for exposures to water contaminants would be seen among smokers alone, and among nonsmokers alone. This would also be true of persons with and without exposures to occupational carcinogens and other exposures.

The wealth of historical exposure information in a case-control interview study permits evaluation of dose-response relationships. A causal interpretation of an association is strengthened by data showing that the risk of individuals increases with the number of years exposed. The time from first exposure to a presumed carcinogenic factor to the appearance of an adverse effect also may be evaluated, and can provide important confirmatory evidence.

We are now on the threshold of obtaining results from carefully conducted case-control interview studies of bladder, colon and rectal cancers which will provide quantitative estimates of risk related to products of chlorination and other water contaminants. Our preliminary evaluation of historical changes in individual water sources suggests that the estimates of risk from the completed case-control mortality studies are conservative, and that the real risks may be much greater. There remains a need for further confirmatory evidence from toxicologic evaluation of the volatile and nonvolatile products of chlorination found in drinking water. Laboratory research which has combined chemical fractionation of bioactive residues isolated from drinking water, combined with *in vitro* biologic assays, is a powerful tool in this regard. The mounting evidence linking chlorination products in community drinking water supplies with elevated risk of human cancer poses a dilemma and a challenge. Quantitative estimates of risk from epidemiologic studies soon to be available will provide a firm and defensible factual basis that can assist in making the challenging decisions of whether or not to further control levels of chlorination by-products and other organic contaminants of public drinking waters.

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